HHS Public Access

Author manuscript

Sex Transm Dis. Author manuscript; available in PMC 2020 September 01.

Published in final edited form as:

Sex Transm Dis. 2019 September ; 46(9): e90. doi:10.1097/OLQ.0000000000001033.

"Proceed with caution in generating evidence in the 'oropharyngeal-anorectal chlamydia hypothesis' in humans"

Teresa A. Batteiger[1], **Stephen J. Jordan**[1], **Evelyn Toh**[2], **David E Nelson**[2,*]

[1]Division of Infectious Diseases, Department of Medicine, Indiana University School of Medicine, Indianapolis

[2]Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis

We thank Leenen *et al.* for their letter (1) regarding our recent manuscript (2). Our results support, but do not prove, the hypothesis that oral exposure is a risk factor for anorectal *Chlamydia trachomatis* (CT) infection. Our manuscript did not report our results as being statistically significant as the underlying study was neither designed nor powered to address the oral transmission hypothesis. We argue that our findings, if proven true, are *clinically significant* as anorectal CT infections were detected in men after carefully controlling for known risk factors. If oral inoculation occurs, our data suggests that it is a rare occurrence in men for reasons that remain to be elucidated.

We wish to address several criticisms that Leenen posed. First, we did not state, nor do we believe, that oropharyngeal chlamydia is the risk factor for anorectal CT infection. We suspect that the mechanism by which oral sex could cause anorectal chlamydia is ingestion of CT-infected vaginal secretions and/or semen. Several observations argue that oropharyngeal chlamydia is not a significant risk factor for anorectal chlamydia: (i) oropharyngeal chlamydia is short-lived; many cases clear before treatment (3), possibly due to the anti-chlamydial properties of saliva (4); (ii) prevalence of oropharyngeal chlamydia is significantly lower than anorectal chlamydia (5); (iii) true oropharyngeal chlamydia prevalence rates may be overestimated as oral sex practices are very common and CT screening tests cannot differentiate established infection from exposure; and (iv) a recent retrospective study failed to find an association between preceding oropharyngeal chlamydia and incident anorectal chlamydia (6). Second, we think it is unlikely that the two rectal CT infections in men without anal sex exposure could be the result of "coincidence". Although false-positivity is one explanation, we proved this not to be true by demonstrating that both rectal swabs had measurable CT loads; one of which was higher than the median CT load of anorectal CT infections that likely arose from direct inoculation. Other possibilities are described in the manuscript.

If correct, the oral hypothesis has important epidemiological and immunological implications. We agree with Leenen *et al.* that a cross-sectional study design cannot prove causality and further studies are warranted. A prospective longitudinal study of rectal

*Address correspondence to nelsonde@indiana.edu.

chlamydia infections in sexually-naïve subjects might reduce confounding from poor-recall of specific sexual behaviors, interim antibiotic treatment, and differing levels of anti-chlamydial immunity. However, epidemiological studies are only as powerful as the variables they capture and are inadequate to fulfill Koch's postulates. Since human challenge studies have demonstrated causality of other treatable STI, and anorectal chlamydia is not associated with disease, oral and rectal chlamydia challenge studies in male volunteers might be warranted to confirm if oral exposures can cause anorectal chlamydia.

References

1. Leenen J, van Liere G, Hoebe C, et al. Proceed with caution in generating evidence in the 'oropharyngeal-anorectal chlamydia hypothesis' in humans. Sex Transm Dis. 2019 (in this issue).
2. Batteiger TA, Jordan SJ, Toh E, et al. Detection of Rectal Chlamydia trachomatis in Heterosexual Men Who Report Cunnilingus. Sex Transm Dis. 2019;46(7):440–5. [PubMed: 31194715]
3. van Rooijen MS, van der Loeff MF, Morre SA, et al. Spontaneous pharyngeal Chlamydia trachomatis RNA clearance. A cross-sectional study followed by a cohort study of untreated STI clinic patients in Amsterdam, The Netherlands. Sex Transm Infect. 2015;91(3):157–64. [PubMed: 25237127]
4. Genc M, Bergman S, Froman G, et al. Antichlamydial activity of saliva. APMIS. 1990;98(5):432–6. [PubMed: 2357343]
5. Chan PA, Robinette A, Montgomery M, et al. Extragenital Infections Caused by Chlamydia trachomatis and Neisseria gonorrhoeae: A Review of the Literature. Infect Dis Obstet Gynecol. 2016;2016:5758387. [PubMed: 27366021]
6. Leenen J, van Liere G, Hoebe C, et al. A longtitudinal study to investigate previous Chlamydia trachomatis infection as a risk factor for subsequent anorectal infection in men who have sex with men (MSM) and women visiting STI clinics in the Netherlands. Epidemiology and Infection. 2019; 147, e214, 1–9. [PubMed: 31364548]